NAVIGATE: improving survival in vulnerable patients with lung cancer through nurse navigation, symptom monitoring and exercise – study protocol for a multicentre randomised controlled trial

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ABSTRACT

Introduction and aim Low socioeconomic position (SEP) has been shown to be strongly associated with impaired lung cancer survival. Barriers related to receiving recommended treatment among patients with lung cancer with low SEP may include adverse health behaviour and limited physical and psychosocial resources influencing the ability to react on high-risk symptoms and to navigate the healthcare system. To address the underlying factors that drive both decisions of treatment, adherence to treatment and follow-up in vulnerable patients with lung cancer, we developed the Navigate intervention. The aim of this randomised controlled trial is to investigate the effect of the intervention on survival (primary outcome), lung cancer treatment adherence, health-related quality of life and other psychosocial outcomes as well as health costs and process evaluation (secondary outcomes) in a study population of vulnerable patients with lung cancer.

Methods and analysis This two-armed multicentre randomised trial will recruit patients from five lung cancer clinics in Denmark identified as vulnerable according to a screening instrument with nine clinical and patient-reported vulnerability criteria developed for the study. We will enrol 518 vulnerable patients ≥18 years old diagnosed with non-small cell lung cancer at all stages with a performance status ≤2. Participants will be randomly allocated to either standard treatment and intervention or standard treatment alone. The Navigate intervention is based on principles from motivational interviewing and includes three components of nurse navigation, systematic monitoring of patient-reported outcomes (PROs) and physical exercise in a person-centred delivery model.

Data will be collected at baseline and 3, 6, 12 months after randomisation using questionnaires, clinical data and physical function tests.

Ethics and dissemination Ethics Committee, Region Zealand (SJ-884/EMN-2020-37380) and the Data Protection Agency in Region Zealand (REG-080-2021) approved the trial. Participants will provide written informed consent. Results will be reported in peer-reviewed journals.

Trial registration number NCT05053997.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Navigate intervention is the first to target survival in vulnerable patients with lung cancer.
⇒ To optimise patient motivation, the Navigate intervention is based on principles from motivational interviewing specifically to engage, focus and set goals for small step changes.
⇒ Participants and health professionals cannot be blinded due to the nature of the intervention.
⇒ The multicentre randomised controlled trial design including patients with lung cancer in all regions of Denmark increases external validity and may facilitate the implementation of the intervention, if results are positive.

INTRODUCTION

Lung cancer continues to be the most commonly diagnosed malignancy in men and women and the leading cause of cancer death worldwide. Although the overall 5-year survival rate for patients with lung cancer has increased during the last decade from 8% to beyond 15% due to advances in medical treatment,2 the prognosis is still poor, especially for patients diagnosed with advanced disease.3

Patients with low socioeconomic position (SEP) have a higher lung cancer incidence and shorter survival after lung cancer compared with patients with high SEP.4,5 Several studies have shown that patients with
lungenkrebs mit niedriger SEP sind weniger wahrscheinlich in erster Linie behandelt zu werden als Patienten mit hoher SEP, unabhängig von der Stadieneinteilung, Histologie und Gesundheitssystem.\textsuperscript{6-11} Unterschiede in der Behandlungsart, Stadieneinteilung und Komorbidität können eine große Proportion der sozialen Ungleichheit in lungenkrebs Prognose zwischen frühem und späterem Stadium erklären.\textsuperscript{8} Daher, in der aktuellen Studie definiert die Vulnerabilität als soziale, verhaltensorientierte und krankheitsbezogene Faktoren, die möglicherweise zu einer schlechteren Adhärenz an lungenkrebs Behandlung beitragen.

Zu unserem Wissen, gibt es bisher keine Studien, die versucht haben, die Effekte von lungenkrebs Adhärenz zu verbessern\textsuperscript{12} oder die Effekte von Rehabilitation und palliativer Behandlung\textsuperscript{13} unter Ausnutzung der Behandlungsbedingungen von Patienten mit lungenkrebs zu einer adäquaten Versorgung und dem nachgelassenen Follow-up. Studien auf anderen Krebsgruppen, die jedoch, wie in der Folgegeprüfung, die Auswirkungen von navigatorischer Pflege berücksichtigen, angezeigt haben, dass die Auswirkungen auf die symptomatische Behandlung, die Anzahl der Arzteinsätze und die Anzahl der Patienten im tertiären Krankenhaus-System, die Behandlungszeiten und der Einsatz von Chemotherapie, und mehr Patienten leben, die bei 1 Jahr (75\% im Vergleich mit 69\% im Kontrollgruppe). Ein ähnlicher RCT von Denis et al.\textsuperscript{28} an Patienten mit fortgeschrittenem lungenkrebs (N=133) hat geprüft, ob web-basierte PROs verglichen mit routinemäßiger Follow-up mit regulären CTs den Patienten in der experimentellen Arm den medianen Überlebenszeit in der experimentellen Arm erheblich verbessert (19 Monate gegenüber 12 Monaten im Kontrollarm)\textsuperscript{29} potenziell durch die Erkennung von Unregelmäßigkeiten und Wiederholungen der Behandlung Adhärenz,\textsuperscript{29} der Effizienz von Follow-up\textsuperscript{29} und der Gesamtoberlebenszeit.\textsuperscript{31} Der Benefiz der PROs hat jedoch noch nicht in vulnerablen Krebspatienten untersucht.

**Nurse navigation**

Nurse navigation ist die Koordination der Krebsbetreuung durch individuell angepasste Unterstützung, um die Implementierung von empfohlenen Behandlungsarten und Follow-ups zu gewährleisten und von Krankenschwestern, die mit der Versorgung von Patienten mit lungenkrebs und dem Gesundheitssystem vertraut sind.\textsuperscript{20,21} Schlüsselkomponenten umfassen die Anbahnung von psychosozialer Unterstützung, die Ausbildung zur Symptommanagement und die Berücksichtigung von relevanten Gesundheits- oder sozialen Treibern.\textsuperscript{20,21} Krankenschwestern haben die klinische Expertise, um die komplettierenden klinischen Herausforderungen zu identifizieren, die durch multidisziplinäre Behandlung von Patienten mit lungenkrebs in der Zeit der Diagnose ablaufen und speziell für Patienten mit multiplen Komorbiditäten.\textsuperscript{22,23} Wir haben gezeigt, dass eine positive Wirkung von Depressions- und depressivem Verhalten 50 psychosozial vulnerablen Patienten mit lungenkrebs in einer Pilotstudie randomisierter kontrollierter Studie (RCT) kombiniert mit Pflegeleistungen in PROs\textsuperscript{24} beobachtet werden kann. Zwei retrospektive beobachtende Studien an Patienten mit lungenkrebs haben Diagnose und Therapieausgangsdaten vor und nach der Implementierung der Pflegeleistungen umso besser die Adhärenz der Pflegeleistung und die Vorschläge für eine optimale Behandlung von lungenkrebs aufgedeckt.\textsuperscript{25,26} Sofern nur ein RCT (N=108) eine Studie, die die Effekte eines zielgerichteten Supportive Care intervention unter Berücksichtigung der Patienten mit inoperablem lungenkrebs\textsuperscript{27} geprüft, die keinen sichtbaren Erfolg in der Vermeidung von gesundheitsbezogenen Bedürfnissen, psychosozialer Morbidität, Depression und krankheitsbezogener Lebensqualität (HRQoL) an Patienten in der Intervention umgehen konnte, die Studie war klein und fokussierten insbesondere die Effizienz von Versorgungs- und Interventionen auf die Adhärenz. Pflegeleistung in lungenkrebs Betreuung kann die Möglichkeit haben, die Proportion von vulnerablen Patienten bei allen Stadien des lungenkrebs zu erhöhen und die Zeit der Lieferung von Behandlung zu verbessern, die Unterstützung strategische Ansätze und die Management von Symptomen verbessern. Obwohl es die Versprechen der Forschung, ist es unbedingt erforderlich, die Effekte der Pflegeleistung auf klinische Auswirkungen zu Patienten mit lungenkrebs zu untersuchen.

**Use of PRO in lung cancer care**

In einem Versuch, die Qualität der Krebsbetreuung und die Aufnahme der Patienten zu verbessern, haben PROs in der Lage gezeigt, den Patienten-pflege-Verkehr, Symptomkontrolle, Patientenzufriedenheit und die Zunahme von SUPPORTIVE CARE.\textsuperscript{17} Basch et al.\textsuperscript{28} haben die Effekte von web-basierten PROs, mit automatisierten Alarms, um die Anzahl von Symptomen bei 766 Patienten mit metastasierter lungenkrebs (25\% Patienten mit lungenkrebs) gefunden. Die Fälle wurden berichtet, dass die mediane Überlebenszeit in der experimentellen Arm erheblich verbessert wurde (19 Monate gegenüber 12 Monaten im Kontrollarm)\textsuperscript{29} potenziell durch die frühzeitige Erkennung von Unregelmäßigkeiten und Wiederholungen der Behandlung Adhärenz,\textsuperscript{29} der Effizienz von Follow-up\textsuperscript{29} und der Gesamtoberlebenszeit.\textsuperscript{31} Der Benefiz der PROs hat jedoch noch nicht in vulnerablen Krebspatienten untersucht.

**Physical exercise in patients with lung cancer**

Ein Cochrane Review von 2019\textsuperscript{32} einschließlich sechs RCTs (N=221 Patienten) zeigte signifikante Effekte von >4 Wochen Training an mindestens einmal pro Woche in der Zeit der Behandlung von Patienten mit fortgeschrittenem lungenkrebs 6 min auf den Umfang der Wanderschaft und HRQoL, aber nicht auf spezifische körperliche und psychosozialen Symptome oder Überleben. Ein neuerer RCT (N=218 Patienten mit inoperablem lungenkrebs) rapportierte signifikante Reduktionen in der Anzahl und der Depression, Verbesserungen in der körperlichen Leistungsfähigkeit (nicht in VO2 peak) und der Erhaltung von sozialen Treibern bei 12 Wochen, zwei und vier Wochen Supervision von cardio- und Leistungstraining programm.\textsuperscript{35} Zwar, auch wenn körperliche Aktivität den Vorteil hat\textsuperscript{32} und sicher\textsuperscript{34} und sicher\textsuperscript{35} an Patienten mit lungenkrebs, die Aufnahme zur Aktivität während der onkologischen Behandlung eine Herausforderung für viele Patienten und besonders für sozial vulnerablen Patienten.\textsuperscript{36} Eine Aktivität des Patienten-individuelle Motivation und die Entwicklung eines Umfelds von Autonomie, Kompetenz und Verwandtschaft kann von krankheitsbedingter Bedeutung sein.\textsuperscript{37} Jedoch, bisherige Studien haben spezifisch effektivere Übungen bei Patienten mit lungenkrebs.

**PROPOSED THEORETICAL FRAMEWORK**

Vulnerabilität in Patienten mit lungenkrebs kann durch multiple Faktoren ausgelöst werden, einschließlich adverser Gesundheitsverhalten, wie Rauchen und Alkoholkonsum, schlechte Physiologie, begrenzte psychosoziale Ressourcen, mangelnde Bildung und Transport.
barriers influencing the ability to adhere to recommended treatment, react to high-risk symptoms and advocate for oneself in the healthcare system. Targeting the complex underlying factors that drive both decisions of treatment as well as adherence to treatment and follow-up are important to improve outcomes for vulnerable patients with lung cancer and intervention development should consider both how to facilitate changes as well as the delivery mode appropriate for the study population.

Activating patient motivation may be especially important to facilitate change in patients who struggle with physical and emotional challenges of cancer treatment and survivorship. Motivational interviewing (MI) has been applied in a number of settings including cancer populations to enhance patient motivation and promote behaviour change such as lifestyle improvements, psychosocial support and cancer-related symptom management.

To optimise delivery mode for vulnerable lung cancer patients, a person-centred and flexible approach to each patient’s needs and resources is essential, for example, proactively providing resources to address transportation barriers, managing symptoms with a telephone-based nurse navigator and maintaining or increasing functional status by home-based exercise sessions supervised by physiotherapist by telephone.

Aims
We aim to examine the added effect of NAVIGATE—a novel intervention including nurse navigation in combination with PRO and physical exercise targeting vulnerable patients with lung cancer in addition to standard care with survival at 12 months after randomisation as primary outcome and adherence to lung cancer treatment, HRQoL and other psychosocial outcomes as well as health costs and process evaluation as secondary outcomes.

METHODS AND ANALYSIS
Setting and participants
The Navigate trial is a multicentre (five Danish hospitals: Zealand University Hospital, Odense University Hospital, Vejle Hospital, Sønderborg Hospital and Godstrup Hospital) two-armed RCT testing the effect of an intervention including nurse navigation, systematic use of PROs and physical exercise targeting vulnerable patients with lung cancer. Recruitment started 1 March 2022 and is anticipated to end 1 March 2024 resulting in end of follow-up on 1 March 2025. The trial protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials and the Template for Intervention Description and Replication.

Eligibility criteria
Patients who fulfil the following criteria are eligible to participate: ≥18 years, diagnosed with non-small cell lung cancer (NSCLC) at all stages, performance status ≤2, eligible for cancer treatment, and vulnerable according to three or more vulnerability criteria from a screening instrument described below. Excluded are patients who are not able to read and understand Danish, with severe untreated psychiatric disorder or cognitive problems preventing informed consent. Each year, approximately 4000 patients are diagnosed with NSCLC at all stages in Denmark, and based on data from pilot testing of the vulnerability screening instrument, we expect that approximately 60% will be screened vulnerable according to three or more criteria. Once included in the trial, there are no exclusions criteria and patients may remain in the study even if they wish to discontinue the exercise programme.

Vulnerability screening instrument
To our knowledge, there are no validated instruments to identify vulnerability in patients with lung cancer defined as being at risk for not adhering to lung cancer treatment. Thus, for the current study we developed an instrument inspired by geriatric assessment tools and through involvement of patients and clinical experts (see the Patient and public involvement section). The screening instrument include nine clinical and patient-reported vulnerability criteria: (1) stage IIIB−IV (from medical journal), (2) comorbidity (somatic or psychiatric) with impact on treatment or comorbidity resulting in hospitalisation within last 3 years (from medical journal), (3) age ≥80 years (from medical journal), (4) performance status =2 (from medical journal), (5) activities of daily living (three patient-reported items regarding difficulties with personal hygiene, taking a walk and climbing stairs), (6) social support (three patient-reported items regarding emotional support as well as support with practicalities at home and transportation), (7) health literacy (three patient-reported items regarding difficulties in understanding healthcare information, instructions from healthcare professionals and filling in forms), (8) transportation related barriers for treatment (three patient-reported items regarding difficulties in reaching the hospital due to lack of transportation, long distance to the hospital or limited energy) or (9) alcohol abuse (three patient-reported items regarding alcohol consumption).

Inclusion procedure and study group allocation
During a 1.5-year period (prolonged if necessary to reach target population), consecutive newly diagnosed (<1 week) patients with lung cancer will be screened for eligibility, invited to participate and randomised by project nurses from clinical trial units at the participating departments. Participants who provide informed consent (online supplemental file B) will be randomised (1:1) to standard treatment plus the intervention (intervention group) or standard treatment alone (control group) as we are interested in evaluating the effect of the intervention compared with what is already offered in the healthcare system. The computer-based randomisation

will ensure a balanced number of random assignments to the two groups in blocks of randomly varying sizes of four or six patients stratified according to study site, performance status and disease stage at diagnosis. No blinding is possible due to behavioural intervention.

**INTERVENTION PROGRAMME**

Based complex intervention guidelines, a review of the literature and feedback from clinical experts and patients, we have developed a patient-centred and flexible intervention programme including nurse navigation, systematic use of PROs and physical exercise (figure 1).

**Nurse navigation**

The manualised nurse navigation programme is based on techniques from MI to:

- Identify patients with high-risk symptoms or worsening in symptoms in order to optimise symptom management.
- Motivate and support patients in making decisions concerning treatment in order to increase treatment initiation and adherence through frequent contact and follow-up.
- Motivate and support patients in health behaviour changes such as increased physical activity, smoking cessation, healthy diet, alcohol moderation by initiating self-management strategies and referral to existing rehabilitation services.

Individual nurse navigation sessions will be performed by 1–2 trained nurses at each department. The nurse navigation manual includes techniques building on MI processes and describes in detail the structure of the first and last sessions as well as an overall format for the sessions in between. A general structure for all sessions include uncovering what is most important for the individual patient, cocreating an agenda and setting goals. Focus is on key MI processes including: engaging, focusing, evoking and planning, and they rely on five central MI communication techniques; asking open questions, affirming the patient, reflective listening, summarising and giving information or advice. The nurse navigation manual includes a total of 16 dialogue tools. To assess and build motivation for change, three MI-based dialogue tools are included to uncover different aspects important for change such as importance, confidence and readiness, to codevelop an overview of potential benefits and harms and to set goals. Moreover, the manual includes four dialogue tools regarding the potential benefits of changing behaviour for example, smoking, alcohol, diet and physical exercise and five dialogue tools supporting value clarification and emotion regulation. The first nurse navigation session will if possible take place at the hospital to enhance a confident relationship. Face-to-face or telephone (by patient’s preference) sessions are then offered weekly during the training programme, bi-weekly after training and while still receiving treatment, and monthly after end of treatment throughout the 1-year intervention. Moreover, the nurse navigator guides patients in self-management strategies according to PROs. Adherence to nurse navigation will be considered sufficient if patients participate in at least 75% of the planned in-person or telephone-based sessions.

**PRO screening**

The aim of collecting PROs is to systematically monitor symptoms and initiate appropriate actions in terms of medical treatment or self-management strategies. PRO screening for symptoms will be collected from diagnosis and up to 1 year bi-weekly through an electronic platform or alternatively through telephone interviews with the nurse-navigator, as per patient preference. Patients will report 12 physical symptoms adapted from the European Organisation for Research and Treatment of Cancer (EORTC). An algorithm has been developed describing recommended actions by the nurse-navigator according to each elevated symptom, for example, appointment with oncologist or self-management of symptom. Adherence to PROs will be considered sufficient if participants report at least 75% PROs.

**Physical exercise**

The aim of the manualised exercise programme is to prevent decline of physical function and enhance level of physical activity to improve eligibility for cancer treatment as well as treatment adherence. The programme will include 24 exercise sessions (two times a week) over 3 months targeting muscle strength, endurance and cardiorespiratory fitness and encouragement to follow the physical activity guidelines for adults with chronic conditions. The sessions can be individual or in smaller groups and will be supervised by 1–4 trained physiotherapists at each department. The exercise manual describe the programme structure, format and progression and the first exercise session will take place at the hospital to ensure the necessary skills to self-manage the programme at home. Participants are encouraged to participate in sessions at the hospital when possible, and any home-based sessions are supported by a video-based exercise guide and telephone supervision by the physiotherapists. Intensity level of the aerobic exercises will be guided using Borg’s rating of perceived exertion scale 6–20.
The exercise programme will consist of the following exercise elements with optional stretching exercises:

- Warm up (5 min) on a stationary bike, as walking or other mode equivalent to this with intensity level 11–13 on Borg scale.
- Aerobic exercise (15 min) on a stationary bike, as walking or other mode equivalent to this with intensity level 14–15 on Borg scale.
- Muscle strength/muscle endurance exercises performed in a sitting position with elastic bands in different strengths (25 min with 3 sets of 15 repetitions). Pull to chest, sit to stand, shoulder press and abdominal crunch.

Progression (encouragement to obtain an intensity level >14 on the Borg scale) in the aerobic exercises will take place at the end of week 5 if possible. Progression in the muscle strength and endurance exercises will be done continuously when patients are able to perform ≥15 repetitions in the last set by using elastic bands with greater resistance. Adherence to exercise will be reported by the physiotherapists or patients using exercise diaries and will be considered sufficient if patients participate in at least 75% supervised or home-based exercise sessions.

**STANDARD CARE**

Patients randomised to the intervention group and the control group will receive standard treatment and care by a nurse and a physician, who sees the patient at treatment schedules and during follow-up, that is, every 3 months for the first year after diagnosis. In some cases, shorter intervals are offered, for example, if the patient has poor performance status. At the first treatment schedule, the patient’s physical, mental and social problems related to the lung cancer diagnosis and treatment are assessed as well as patient-reported needs of support related to diet, smoking, alcohol and exercise using a standardised questionnaire. The patient’s response is used to assess any side effects or rehabilitation needs as well as to refer to relevant rehabilitation services. The nurse will continue to assess potential side effects or psychological or social issues during treatment and follow-up and if needed refer patients to a dietitian or social worker. The treating physician refers to a specialist palliative care team if needed.

**Patient and public involvement**

Patients were involved in both the development of the vulnerability screening instrument and the intervention content and procedures.

The vulnerability screening instrument was first discussed at a workshop including clinical experts in lung cancer and a patient organisation representative. The draft-screening instrument was then discussed against existing geriatric assessment tools screening for increased risk for treatment complications, prediction of symptom burden and survival among older patients with lung cancer as well as expert interviews with seven lung cancer experts and patient interviews with 10 patients with lung cancer in terms of completeness, relevance, comprehension, format and setting. Finally, we pilot tested the vulnerability screening procedure in feasibility questionnaires among 20 patients and found that 65% patients (N=13) had three or more criteria and would be considered vulnerable.

To ensure clinical and patient relevance, the study design and procedures including barriers to trial recruitment and data collection as well as the intervention components, were discussed at the workshop as well as through the patient interviews. Overall, patients found the intervention components highly relevant, but expressed concerns about transportation barriers. This resulted in replacement of in-person meetings at the hospital with flexible telephone-based nurse navigation and home-based exercise sessions. Finally, we will evaluate the study and intervention procedures as well as adherence goals within an ongoing feasibility intervention study including 15 patients with lung cancer at Zealand University Hospital, which may result in further adjustments. Any important modifications will be added at ClinicalTrials.gov. We will inform study participants about the study results through email or letter, as per patient preference.

**DATA COLLECTION**

Data from both groups on the primary outcome survival and treatment factors (table 1) will be obtained from the Lung Cancer Clinical Database and individual medical records.

Both groups will fill out questionnaires (table 1) at baseline prior to randomisation as soon as possible and within 1.5 months after diagnosis (T0), and 3 months (T1), 6 months (T2) and 12 months (T3) after diagnosis (figure 1). Scales such as EORTC52 53 and European Quality of life Questionnaire-5 Dimensions-5 Levels54 will be scored according to published manuals. Considering that participating patients are vulnerable with limited resources, we will proactively support patients in responding to questionnaires electronically, on paper or via telephone. If participants do not fill in the questionnaires at prespecified times, they will receive a reminder by email or telephone. Objective measures of physical function and activity (6 min walk test,55 30 s chair stand test56 and a hand grip strength dynamometer test57 58 will be assessed at T0, T1 and T3. We will allow assessment of physical function postrandomisation at T0 to ensure prompt enrolment into the study. Data will be confidently and safely stored at Region Zealand and the Danish Cancer Society Research Center using the electronic platform REDCAP.59

In order to perform cost-effectiveness analyses, use of health services including all outpatient visits to any healthcare clinic will be retrieved from the Danish National Patient Registry and medical records while information on disability and productivity loss (sick leave, disability pension and retirement pension) will be obtained from...
the Integrated Database for Labour Market Research. The cost-analyses will also include nurse navigator sessions and supervised physiotherapy as outpatient visits to estimate the cost of the intervention.

**INTERVENTION FIDELITY**

To enhance fidelity *prior to the study*, all nurse-navigators will enrol in a 5-day training course focusing on social inequality in lung cancer, lung cancer treatment, symptoms of recurrence, physical and psychological late effects, research methodology, health behaviour and MI including training the techniques included in the manual. Physiotherapists will attend a 1-day training course focusing on the effects of exercise among patients with lung cancer, the exercise manual and the physical tests. To enhance fidelity *during the study*, nurses and physiotherapists will receive monthly supervision regarding techniques and study procedures. To evaluate fidelity, nurse navigators will use a checklist to document use of tools from the nurse-navigator manual, use of PROs and the number and length of patient sessions and physiotherapists will use exercise diaries to document use of the exercise programme. In addition, nurse navigator sessions will on patient consent be audio-recorded to assess implementation fidelity (app. 10% of sessions) to MI spirit and techniques using the Motivational Interviewing Treatment Integrity Code. Finally, to evaluate mechanisms of intervention impact, observations by a research assistant of nurse and excise sessions (N=10) as well as qualitative interviews with participants (N=10) and focus group interviews with nurse navigators (N=5) and physiotherapists (N=5) concerning intervention facilitators and barriers.

**POWER CONSIDERATIONS**

The power calculation is based on a presumed improvement in 1-year survival of 13% corresponding to half of the effect in the study by Denis *et al*. Assuming that patients in the control group have a 50% 1-year overall survival and the intervention group have 63% 1-year overall survival and a 15% withdrawal probability, then we have 80% power to detect a significant difference using a log-rank test with a total of 518 patients that is, 259 per group. Assuming that 60% (N=865) will be considered vulnerable with three or more vulnerability criteria (based on numbers from the pilot testing of the screening instrument (N=20)) and a conservative 50% participation rate, a total of 1730 patients will be invited.

**STATISTICAL ANALYSES**

Descriptive statistics will be used to estimate the frequencies, means and SD of the baseline patient, clinical and treatment characteristics including any adverse events. Analyses will be based on intention-to-treat with primary analyses testing the effect of the intervention on overall 1-year survival defined as time from randomisation to death with censoring at withdrawal or end of follow-up.

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Table 1  Data from medical journals, the lung cancer clinical database and electronic questionnaires

<table>
<thead>
<tr>
<th>Variables</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical journal, the lung cancer clinical database and the Civil Registration System</td>
<td>Date of skipped lung cancer treatments or delays if any, and dose administered</td>
</tr>
<tr>
<td>Lung cancer treatment adherence</td>
<td></td>
</tr>
<tr>
<td>Lung cancer diagnosis</td>
<td>Histology, stage and performance status</td>
</tr>
<tr>
<td>Standard treatment initiated</td>
<td>Surgery, chemotherapy, radiotherapy, immunotherapy and medical treatment of side-effects</td>
</tr>
<tr>
<td>Vital status</td>
<td>Date of death or date last registered in live</td>
</tr>
<tr>
<td>Municipality rehabilitation</td>
<td>Referral status</td>
</tr>
<tr>
<td>Follow-up adherence</td>
<td>Date of non-response, if any</td>
</tr>
<tr>
<td>Comorbidities and medical treatment</td>
<td>Date of diagnosis of comorbidities and medical treatment for comorbidities, if any</td>
</tr>
<tr>
<td>Patient-reported factors related to vulnerability</td>
<td>Activities of daily living, social support, health literacy, barriers for treatment and alcohol abuse</td>
</tr>
<tr>
<td>Questionnaire</td>
<td></td>
</tr>
<tr>
<td>Demographics (baseline only)</td>
<td>Age, gender, partner, education, job</td>
</tr>
<tr>
<td>HRQoL</td>
<td>EORTC QLQ-C30+lung QLQ-LC13+5Q-5D-5L</td>
</tr>
<tr>
<td>Health behaviour</td>
<td>Alcohol, smoking and physical activity measured by single-item questions</td>
</tr>
<tr>
<td>Self-activation/self-efficacy</td>
<td>Measured by single items from PAM and HEIQ</td>
</tr>
<tr>
<td>Rehabilitation services</td>
<td>Measured by a single item question</td>
</tr>
</tbody>
</table>

EORTC QLQ-C30, The European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; HEIQ, Health Education Impact Questionnaire; Lung QLQ-LC13, Quality-of-life Questionnaire Lung Cancer 13; PAM, Patient Activation Measure; 5Q-5D-5L, European Quality of life Questionnaire-5 Dimensions-5 Levels.
Overall survival in the two groups will be estimated by the Kaplan-Meier method and compared by the log-rank test. In the primary analysis, Cox proportional hazards model will be used to estimate the HR and 95% CIs for time to death in the intervention group versus the control group adjusted for the stratification factors in the randomisation (study site, performance score and disease stage at diagnosis).

In secondary analyses, we will test the effect of the intervention on overall survival at 3 and 6 months from randomisation using the same survival model as described for the primary analysis. Moreover, the longitudinal measurements of lung cancer treatment adherence, symptom burden, HRQoL, health behaviour, self-efficacy, self-activation and use of rehabilitation services at 3, 6 and 12 months from randomisation will be compared between the two groups using methods that take into account informative censoring due to withdrawal and truncation by death as described by previous studies. Analyses will be adjusted for the randomisation stratification factors. If there is a substantial amount of missing data due to non-response, missing data techniques will be employed. Cost-effectiveness of the intervention versus standard care will be assessed at 12 months follow-up with the ratio of the net healthcare costs to net quality-adjusted life years between the two groups.

In sensitivity analyses for the primary and secondary outcomes, we will adjust for potential imbalances in variables such as age, stage and gender at baseline. To identify subgroups of patients who may especially benefit from the intervention we will examine effect modification according to for example, gender, age and specific vulnerability criteria both in the survival model and in the longitudinal models. Adherence to the intervention (≥75% vs <75%) will be explored in the intervention group by estimating the proportion of adherence. We will further explore the potential of full adherence to the intervention by the use of methods for causal inference.

ETHICS, DISSEMINATION OF RESULTS AND PERSPECTIVES OF THE TRIAL

Ethical considerations

The study has been approved by and follows the requirements from The National Committee on Health Research Ethics (Ref no SJ 884, EMN-2020-37380). Participation will be voluntary, and patients will receive written and verbal information about the study and sign written informed consent before study participation. Participants will have the right to withdraw from the study at any time without giving any reason and with no consequences for continued treatment. Participants will not be restricted from any activities or treatments outside the study.

We cannot rule out that weekly collection of physical and psychological symptoms during treatment may lead to increased risk for uncertainty and anxiety. All participants in the study are instructed to report if they experience any side effects, risks or harms associated with study participation. There are no known circumstances that may lead to termination of this study or that participants will be excluded from study participation.

Dissemination of study results

All papers related to the study will be published in accordance to the Consolidated Standards of Reporting Trials statement in relevant peer-review journals. The study results will be presented at international conferences and at the website of the Danish Research Center for Equality in Cancer, COMPAS (www.compas.dk). Moreover, we will communicate the results to broader groups in the society in a video format at social media platforms.

DISCUSSION

This protocol describes the first RCT aimed to improve survival after lung cancer by targeting vulnerable patients with lung cancer. The underlying factors that drive social inequality in lung cancer prognosis are multifactorial and calls for a complex intervention with a person-centred and flexible approach for reaching this study population. The overarching challenges related to the study include recruitment of patients and attrition during the exercise programme. We plan to address these challenges by applying a high degree of patient involvement in the development phase and by assigning the recruitment of patients to trained research nurses from clinical research units at each participating department. To increase adherence to the exercise programme patients may use home-based sessions with telephone-based supervision by physiotherapists. Moreover, due to the nature of the intervention, participants and health professionals cannot be blinded, which may introduce measurement bias of the self-reported secondary outcomes. It was not possible to include patients who are unable to read or speak Danish, as we were not able to ensure adequate translation services in the intervention and the study procedures. As non-Danish speaking patients may represent some of the most vulnerable patients, this is expected to limited generalisability of our results to this group. Finally, the applied cut-off for the vulnerability screening instrument for identifying patients at risk for not completing treatment before trial initiation was established in a feasibility study and further psychometric evaluation is planned.

Results from the Navigate trial hold great potential for improving supportive care to vulnerable lung cancer patients with fragile social support, low health literacy and complex needs. The primary success criteria is that patients in the intervention group experience clinically relevant improvements in survival and symptoms. The ultimate success criteria will be implementation of the intervention at lung cancer clinics in Denmark, if results support it. By applying a high degree of patient involvement in the development phase and evaluating the intervention in a national multicentre setting, we hope to optimise the potential for implementation. Still, implementation at a national level would require an
implementation plan, training of nurses based on the Navigate manual as well as training of physiotherapists to perform the exercise programme.

The Navigate trial has the potential to make an international contribution to clinical practice by providing clinicians with a new comprehensive model of care targeting vulnerable patients with lung cancer. We believe this model of care may also be relevant for other vulnerable patients with cancer and chronic diseases. With the Navigate intervention, we hope to take the first important steps towards reducing inequality in our healthcare system by giving vulnerable patients with lung cancer a greater possibility to achieve the same treatment outcomes as the more resourceful patients.

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5The Danish Lung Cancer Registry, Odense University Hospital, Odense, Denmark
6Center for Clinical Epidemiology and Research Unit of Clinical Epidemiology, Odense University Hospital, Odense, Denmark
7Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts, USA
8Unit for Clinical Alcohol Research, University of Southern Denmark, Odense, Denmark
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10Department of Physiotherapy and Occupational Therapy, Zealand University Hospital, Roskilde, Denmark
11Department of Physiotherapy and Occupational Therapy, The Research Unit PROFrez, Næstved-Slægelse-Ringsted Hospitals, Slagelse, Denmark
12Department of Sports Science and Clinical Biomechanics, Research Unit for Musculoskeletal Function and Physiotherapy, University of Southern Denmark, Odense, Denmark

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Contributors PEB, SOD, EJ, RKV, LBJ and STS and RL contributed substantially to the concept and design of this trial. RL, RKV and PEB developed manuals for recruitment, assessment and nurse navigation. LBJ, STS, RL and PEB developed manual for the physical tests and exercise programme. PEB, RKV and RL developed written information for participants. RL, PEB and SOD contributed with applications for grants, and approval assignments. PEB, RKV and RL introduced and supervised the recruitment, assessment and intervention concepts and procedures to all involved physiotherapists and nurses, and will lead the data collection. EAWA performed the power analysis. EAWA and SR contributed substantially with input to the design and statistical analyses. RL and PEB drafted the manuscript. All authors (RL, SOD, EJ, RKV, MI, KMF, AL, ASN, EAWA, SR, LBJ, STS and PEB) provided intellectual feedback to the manuscript and approved the final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES


Halgren MO, Kjaer TK, Dalton SO. Hvidbog - Social ulighed i kræft i Danmark. *2019*.


Supplementary file A

World Health Organization trial registration data set for ‘NAVIGATE – Improving survival in vulnerable lung cancer patients through nurse navigation, symptom monitoring and exercise: study protocol for a multicenter randomized controlled trial’

<table>
<thead>
<tr>
<th>Data category</th>
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<tr>
<td>Date of registration in primary registry</td>
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<tr>
<td>Secondary identifying numbers</td>
<td>None</td>
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<tr>
<td>Source(s) of monetary or material support</td>
<td>The Danish Cancer Society ‘Knæk Cancer’ (grant no. R223-A13094-18-S68) The Novo Nordisk Foundation (grant no. NNF20OC0064570) The Independent Research Fond (grant no. 1030-00414B) Danish Research Center for Lung Cancer Region Southern Denmark and Region Zealand Research Fond The Danish Comprehensive Cancer Center.</td>
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<tr>
<td>Primary sponsor</td>
<td>Mads Nordahl Svendsen, Department of Clinical Oncology and Palliative Care, Zealand University Hospital</td>
</tr>
<tr>
<td>Secondary sponsor(s)</td>
<td>None</td>
</tr>
<tr>
<td>Contact for public queries</td>
<td>Rikke Langballe, project coordinator + 45-35257972 <a href="mailto:ril@cancer.dk">ril@cancer.dk</a></td>
</tr>
<tr>
<td>Contact for scientific queries</td>
<td>Rikke Langballe, project coordinator + 45-35257972 <a href="mailto:ril@cancer.dk">ril@cancer.dk</a></td>
</tr>
<tr>
<td>Public title</td>
<td>NAVIGATE – Improving survival in vulnerable lung cancer patients</td>
</tr>
<tr>
<td>Scientific title</td>
<td>NAVIGATE – Improving survival in vulnerable lung cancer patients through nurse navigation, symptom monitoring and exercise: study protocol for a multicenter randomized controlled trial</td>
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<tr>
<td>Countries of recruitment</td>
<td>Denmark</td>
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<td>Health condition(s) or problem(s) studied</td>
<td>Social inequality in lung cancer</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Intervention: Patients' symptoms are systematically monitored by use of bi-weekly patient reported outcomes and nurse navigators will initiate appropriate actions in terms of medical treatment or guidance of self-management strategies. Nurse navigators will motivate and support patients in health behavior changes and in self-managing their treatment and symptoms, and, if relevant, refer to existing rehabilitation services at the hospital or at the local rehabilitation center. Physiotherapists will supervise a training program aimed at improving patients' physical function and thus potentially surgery and overall treatment adherence and outcomes.</td>
</tr>
<tr>
<td>Comparator: Standard treatment and care by a nurse and a physician, who sees the patient at treatment schedules and during follow-up, i.e. every three months for the first year after diagnosis</td>
<td></td>
</tr>
<tr>
<td>Key inclusion and exclusion criteria</td>
<td>Inclusion criteria:</td>
</tr>
<tr>
<td></td>
<td>• &gt; 18 years</td>
</tr>
<tr>
<td></td>
<td>• Diagnosed with Non-small-cell lung cancer at all stages</td>
</tr>
<tr>
<td></td>
<td>• Performance status ≤2</td>
</tr>
<tr>
<td></td>
<td>• Eligible for cancer treatment</td>
</tr>
<tr>
<td></td>
<td>• Vulnerable according to pre-defined criteria</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Severe psychiatric disorder or cognitive problems preventing informed consent</td>
</tr>
<tr>
<td></td>
<td>• Not able to read and understand Danish</td>
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<tr>
<td>Study type</td>
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<tr>
<td>Allocation: randomized</td>
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<tr>
<td>Intervention model: parallel assignment</td>
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<tr>
<td>Masking: none</td>
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<tr>
<td>Primary purpose: testing the effect of the intervention compared to standard care and treatment</td>
<td></td>
</tr>
<tr>
<td>Date of first enrolment</td>
<td>March 2022</td>
</tr>
<tr>
<td>Target sample size</td>
<td>518</td>
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<tr>
<td>Recruitment status</td>
<td>Recruiting</td>
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<tr>
<td>Primary outcome(s)</td>
<td>Survival (time frame: 12 month)</td>
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<tr>
<td>Key secondary outcomes</td>
<td>Changes in survival at 3 and 6 months as well as adherence to cancer treatment, health related quality of life and health behavior (time frame: baseline, 3, 6 and 12 months)</td>
</tr>
<tr>
<td><strong>Ethics Review</strong></td>
<td>Ethics Committee, Region Zealand (SJ-884 / EMN-2020-37380) and the Data Protection Agency in Region Zealand (REG-080-2021) approved the trial.</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td><strong>Completion date</strong></td>
<td>March 2025 (Estimated)</td>
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<tr>
<td><strong>Summary results</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>IPD sharing statement</strong></td>
<td>There is no plan to share individual participant data</td>
</tr>
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</table>
Supplemental file B: Informed consent form

Purpose
We wish to investigate whether an individually tailored program with a nurse navigator can help more patients through their treatment for lung cancer. The nurse navigator offers regular support and keep an eye on the symptoms you may experience during and after treatment. The physiotherapist will guide you through an exercise program with the aim of improving your physical and mental condition during treatment.

If you choose to participate in the project, we process the following categories of personal data about you:

Standard personal data
- Name
- Address
- Telephone number
- E-mail
- Cohabitation status
- Labour market attachment
- Age
- Gender

Sensitive personal data
- Diagnosis, disease stage and time of diagnosis
- Treatment, medication and completion of treatment
- Responses from questionnaires concerning your physical and mental health, your health behavior, quality of life and how you manage your disease
- CPR number

Data controller
Region Zealand and the Danish Cancer Society are joint data controllers for processing the personal data we have received about you. You will find the contact details below.

Region Zealand
Alleen 15,
4180 Sorø
E-mail: datatilsyn@regionsjaelland.dk
Region Zealand’s data protection advisor: dpo-funktion@regionsjaelland.dk

The Danish Cancer Society
Strandboulevarden 49,
2100 Copenhagen Ø
CVR 55629013
E-mail: persondata@cancer.dk
The Danish Cancer Society’s data protection advisor: dpo@cancer.dk
Telephone: 35257500
**Project manager**
The project manager is the person who is responsible for the implementation of the project that you participate/have participated in. You will find contact information below.

**Susanne Oksbjerg Dalton, professor and senior physician**
Department of Clinical Oncology and Palliative Care, Zealand University Hospital, Rådmandsengen 5, 4700 Næstved
E-mail: sdalt@regionsjaelland.dk
Telephone: 30381540

**Pernille Envold Bidstrup, senior researcher and head of research group**
The Danish Cancer Society
Strandboulevarden 49, 2100 Copenhagen Ø
E-mail: pernille@cancer.dk
Telephone: 35257600

**Declaration from the participant**
I have received written and oral information and I know enough about the purpose, method, advantages and disadvantages to agree to participate. I know that participation is voluntary and that I can always withdraw my consent without justification by contacting Rikke Langballe, e-mail: ril@cancer.dk, telephone 35257972, without losing my current and future treatment rights.

☐ I give consent to participate in the research project Navigate – Individual support for lung cancer treatment – including consent to have information about me collected from my medical record and questionnaires. I have received a copy of this consent form as well as written information.

☐ I give consent to use audio recordings during sessions with the nurse navigator

☐ I give consent to a research assistant present can participate in nurse and training sessions to follow-up on how these sessions are carried out.

Name: ________________________________

Telephone number: ________________________________

E-mail: ________________________________

CPR-number: ________________________________

Signature: ________________________________ Date: ________________

☐ I wish to be informed about the results of the research project as well as possible consequences for me.
Declaration from the person giving oral information:
I declare that the participant has received oral and written information about the research project. It is my belief that sufficient information has been provided for a decision to be made about participation in the research project.

Name of the person who has provided information: ________________________________

Date: ______________ Signature: ________________________________